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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/694,432	10/27/2003	Kathleen C.M. Campbell	SIU 7399	8934

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SENNIGER POWERS
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EXAMINER	
ROYDS, LESLIE A	
ART UNIT	**PAPER NUMBER**
1614	

DATE MAILED: 03/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/694,432	CAMPBELL, KATHLEEN C.M.	
	Examiner	Art Unit	
	Leslie A. Royds	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 November 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9 and 11-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9 and 11-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *07/27/05 &11/17/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-9 and 11-29 are presented for examination.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office Action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission and Declarations under 37 C.F.R. 1.132 of Kathleen C.M. Campbell and Prasad Sunkara, each filed on November 17, 2005, have each been received and entered into the present application.

Applicant's Submission of Cited References 8, 22, 34-37, 64 and 66

Applicant's submission of the cited references numbered 8, 22, 34-37, 64 and 66 on the Information Disclosure Statement filed March 4, 2005 have each been received and entered into the application. Applicant's submission of the Information Disclosure Statement (IDS) filed November 17, 2005, identical to the IDS filed March 4, 2005, was also received and entered into the application. Accordingly, and as reflected by the attached, completed copy of form PTO/SB/08A (eight pages total), the Examiner has only considered those newly provided references, namely the references designated as 8, 22, 34-37, 64 and 66 on the IDS dated November 17, 2005. The references designated as 1-7, 9-21, 23-33, 38-63, 65 and 67-75 on the IDS dated November 17, 2005 have already been considered by the previous Examiner and recordation to that effect can be noted on the IDS dated March 4, 2005.

Applicant's Information Disclosure Statement dated July 27, 2005 (two pages) has also been received and entered into the application. As reflected by the attached, completed copy of form PTO/SB/08A, the Examiner has considered the cited references.

Applicant's Claim for Priority under 35 U.S.C. §120

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. §120 is acknowledged. Applicant is reminded that the later-filed application must be an application for patent for an invention that has been disclosed in the parent application. The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

Applicant has failed to comply with the conditions for receiving the benefit of an earlier filing date under 35 U.S.C. §120 insofar as it is claimed to U.S. Patent Application No. 08/942,845, filed October 2, 1997, because the subject matter disclosed in this application does not contain sufficient enablement as required under 35 U.S.C. 112, first paragraph, for the presently claimed subject matter. Specifically, the disclosures of this application to which the present application claims priority does not reasonably provide enablement for or disclose or suggest a method of treating ototoxicity, neurotoxicity, alopecia, gastrointestinal disorders, or reduced survival in a patient exposed to radiation for a time and at an intensity sufficient to result in such conditions using the presently claimed methionine compound.

However, the disclosure of U.S. Patent Application No. 09/057,065, filed April 8, 1998 does contain sufficient support and enablement as required under 35 U.S.C. 112, first paragraph, for the presently claimed subject matter. Accordingly, claims 1-9 and 11-29 are properly granted

the effective filing date of U.S. Patent Application No. 09/057,065 (April 8, 1998).

Claim Rejection - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9 and 11-29 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of alopecia or oral mucositis using D-methionine, does not reasonably provide enablement for the prevention of ototoxicity, neurotoxicity, alopecia, gastrointestinal disorders or reduced survival using any one of the claimed methionine compounds other than D-methionine, nor does it reasonably provide enablement for the treatment of ototoxicity, neurotoxicity, gastrointestinal disorders or reduced survival using any one of the claimed methionine compounds, for the reasons already made of record in the previous Office Action dated May 17, 2005 at page 2 and further in view of the following remarks made herein.

Response to Applicant's Remarks Regarding Enablement

Applicant submits that a person of ordinary skill would have been likely to refer to a technical dictionary rather than a general purpose dictionary and cites Stedman's Medical Dictionary (26th Edition, 1995) to define "prevent" or "preventive" as "to come before" and relies on The Signet/Mosby Medical Encyclopedia (1987) to define treatment as, for example, a

method of fighting, reducing or preventing a disease, disorder or injury (see page 3 of remarks). Applicant states that the administration of the protective agent could be prior to, simultaneous with or subsequent to the onset of the condition, but neither "treating" nor "relief" requires a cure, and "treating" is not limited to care of an existing condition. Applicant further relies upon the Declaration under 37 C.F.R. 1.132 of Prasad Sunkara to show that treatment with D-methionine before or after radiation exposure reduced the incidence of hair loss and increased the survival of jejunal crypt cells associated with radiation induced oral mucositis. Applicant also relies upon the Declaration under 37 C.F.R. 1.132 of Kathleen Campbell, which presents0 preliminary data showing no statistically significant difference in the ABR threshold shift between rats receiving D-methionine and radiation and those rats receiving radiation alone, but asserts that refined experimental conditions would show such a difference.

Applicant's remarks and the Declarations under 37 C.F.R. 1.132 of Prasad Sunkara and Kathleen Campbell have each been carefully considered, but fail to be persuasive in establishing error in the propriety of the present rejection.

In support of the present rejection of the claims lacking sufficient enablement to demonstrate how to make and use the full scope of the claimed invention, the Examiner relies upon *In re Marzocchi et al.*, 169 USPQ 367 (CCPA 1971):

"[A] [s]pecification disclosure which contains teaching of manner and process of making and using the invention in terms corresponding to the scope and to those used in describing and defining subject matter sought to be patented must be taken as in compliance with the enabling requirement of first paragraph of 35 U.S.C. 112 *unless there is reason to doubt the objective truth of statements contained therein which must be relied on for enabling support;* assuming

that sufficient reasons for such doubt exists, a rejection for failure to teach how to make and/or use will be proper on that basis, such a rejection can be overcome by suitable proofs indicating that teaching contained in the specification is truly enabling." (emphasis added)

Applicant is also directed to the MPEP at §2164.08. All questions of enablement are evaluated against the claimed subject matter. Concerning the breadth of a claim relevant to enablement, the only relevant concern is whether the scope of enablement provided to one skilled in the art by the disclosure is commensurate with the scope of protection sought by the claims. The determination of the propriety of a rejection based upon the scope of a claim relative to the scope of enablement involves the determination of how broad the claim is with respect to the disclosure and the determination of whether one skilled in the art is enabled to make and use the *entire scope* of the claimed invention without undue experimentation.

Regarding the issue of prevention, Applicant argues against the use of a general purpose dictionary as the basis for their plain meaning, stating that one of ordinary skill in the art would look rather to a technical dictionary than a general dictionary. In response thereto, the Examiner notes that claimed terms must be given their plain meaning in accordance with the MPEP at §2111.01. In light of the direction of the MPEP at §2111.01, it remains that the citation of such a general dictionary as the basis for the plain meaning of such terms would not have been improper, nor would it have been outside the purview of the skilled artisan. However, even if Applicant's assertion is correct, namely that one of ordinary skill in the art would have looked to a technical dictionary rather than a general purpose dictionary, it remains that the term "preventing" still, in its broadest reasonable interpretation, circumscribes a method of absolute success.

Though Applicant has invoked the particular definition of "prevent" or "preventive" from Stedman's Medical Dictionary (26th Edition, 1995), it remains that claimed terms must be given their plain meaning in accordance with the MPEP at §2111.01. In light of such, the Examiner has relied upon Stedman's Medical Dictionary (22nd Edition) to define the word "preventive", which Stedman's Medical Dictionary defines as "prophylactic, warding off disease...anything that arrests the threatened onset of disease" (see page 1017). Stedman's Medical Dictionary defines "prophylactic" as "an agent...that acts as a preventive against any disease" (see page 1025).

Such definitions are given their broadest reasonable interpretation in accordance with the MPEP at §2111. Thus, while it is acknowledged that Stedman's does not explicitly state that prevention requires absolute success, the very nature of "arresting the threatened onset of disease" would indicate, in its broadest sense, that the incidence of developing a disease would be 0% and there would be a reasonable guarantee that such a disease would never develop. Such a situation is sufficiently unusual that the specification would need to show data to establish that a disease or disorder, such as ototoxicity, neurotoxicity, alopecia, gastrointestinal disorders or reduced survival, would be kept from ever occurring simply by the administration of the presently claimed active methionine or methionine-like compound. Because absolute success is not reasonably possible with most diseases or disorders, especially conditions as complex and poorly understood as those presently claimed, the specification or the presently submitted Declarations under 37 C.F.R. 1.132, which all lack an objective showing that the presently claimed disorders could actually be prevented, is viewed as lacking an enabling disclosure of the same, despite Applicant's assertions to the contrary.

Applicant has further relied upon the Declarations of Prasad Sunkara and Kathleen Campbell in support of the conclusion that there is sufficient disclosure and evidence to presently claim the prevention of such conditions.

Applicant states, on the record, "These data show that treatment with D-methionine before or after radiation exposure reduced the incidence of hair loss in mice undergoing experiments related to the prevention of radiation induced oral mucositis. In addition to hair loss, administration of D-methionine to mice increased the survival of jejunal crypt cells as measured per jejunal circumference upon whole body radiation exposure. This increased jejunal crypt cell survival with D-methionine administration upon whole body radiation exposure indicated that gastrointestinal side effects are decreased as compared to exposure to whole body radiation alone." (see page 3 of remarks)

Such evidence provided in the Declaration of Prasad Sunkara is, respectfully, insufficient to support Applicant's claim that prevention of alopecia or gastrointestinal disorders, in general, could be achieved. The Examiner notes that the very use of the phrase "reduced the incidence" is not comparable to absolute prevention. The very use of the words "reduced the incidence" indicates a margin of error, in that administering D-methionine may significantly reduce the incidence of hair loss, but that it is not guaranteed to provide complete and absolute protection from the development of such a condition. Furthermore, Applicant has not identified the number of mice studied that demonstrated a reduced incidence of hair loss and refers to "attached Figure 1" as showing the results of the study. Such a figure has not been provided. In the absence of such a figure, the importance of the results cannot be afforded the significance that Applicant has requested. In particular, it is noted that if the reduced incidence of hair loss was merely

demonstrated in one mouse alone, such would most certainly not be sufficient to then claim the absolute prevention of alopecia in general.

Similarly, the Examiner notes that the phrase "increased survival of jejunal crypt cells" is also not comparable to absolute prevention. The very use of the words "increased survival" indicates that while many or most of the cells have increased survival, not all cells exhibit such an increase in survival and, therefore, are susceptible to developing oral mucositis, if a sufficient number of cells with shortened survival exist. In other words, the fact that the increased survival of such cells may reduce the incidence of developing oral mucositis does not guarantee that complete and absolute protection from ever developing such a condition will occur.

Applicant further states, on the record, "In addition to data showing decreased hair loss and increased jejunal crypt cell survival, Applicant herewith submits a declaration of the inventor, Dr. Kathleen C.M. Campbell, which presents preliminary data regarding the administration of D-methionine to male Wistar rats before radiation exposure. These data show that D-methionine administration has an effect on the levels of various cochlear antioxidants and enzymes (e.g., glutathione, oxidized glutathione, superoxide dismutase, catalase, glutathione peroxidase, and glutathione reductase). **But, this study did not show a significant difference in the ABR threshold shift between the rats receiving D-methionine and radiation exposure and the rats receiving radiation exposure alone. Because these data were preliminary, Dr. Campbell believes that refined experimental conditions would show a difference in auditory brainstem response (ABR) threshold between the rats receiving D-methionine and radiation and the rats receiving radiation alone.**" (emphasis added)

Such evidence is clearly not sufficient to even enable the treatment of ototoxicity (e.g.,

hearing loss) as it results from radiation exposure, let alone the prevention of such a disorder. Applicant has clearly not demonstrated any statistically significant difference between the control mice and those that received both radiation and D-methionine, which not only casts significant doubt on the ability of such a combination to effectively *treat* ototoxicity from radiation exposure, but also raises the question that if such a therapeutic combination is incapable of even *treating* such a disorder, then it most certainly is not able to *prevent* such a disorder, since the standard for showing prevention of a condition is much higher than the showing required to simply claim treatment. In other words, if the data shown fails to adequately demonstrate that treatment of the disorder can be accomplished, then it necessarily is not sufficient to be representative of prevention.

Thus, in conclusion, the present disclosure fails to enable one of ordinary skill in the art how to use the invention commensurate in scope with the claims. In particular, the specification lacks sufficient enablement for the prevention of ototoxicity, neurotoxicity, alopecia, gastrointestinal disorders or reduced survival.

The present specification does not provide any exemplary evidence as to how to use the invention commensurate in scope with the claims. The sole evidence directed towards how to use the presently claimed invention has been provided in the Declarations under 37 C.F.R. 1.132 of Kathleen Campbell and Prasad Sunkara. As previously stated above, both the specification and each of the submitted Declarations, respectfully, conspicuously lack evidence to support the contention that the presently claimed invention could be used to achieve the prevention of ototoxicity, neurotoxicity, alopecia, gastrointestinal disorders or reduced survival, in general. In addition, the specification also conspicuously lacks sufficient support as to how to use the

presently claimed invention insofar as it reads upon the treatment of ototoxicity, neurotoxicity, alopecia, gastrointestinal disorders or reduced survival.

The evidence proffered in the 1.132 Declarations of K. Campbell and P. Sunkara fails to cure this deficiency. In particular, Applicant has failed to show any statistically significant difference in auditory function for the group of control mice (i.e., those that received only radiation) versus the experimental group of mice (i.e., those that received both D-methionine and radiation). In essence, such results amount to a definitive demonstration that the presently claimed compound(s) (i.e., D-methionine) cannot be used for the treatment of ototoxicity resulting from exposure to radiation. While Applicant states that refined experimental conditions would demonstrate a difference between those rats that received D-methionine and radiation and those rats that received radiation alone (see page 4 of the remarks), such a statement amounts to no more than an unsubstantiated projection and, therefore, cannot be afforded the significance that Applicant has urged. In light of such, Applicant has not adequately directed one of ordinary skill in the art how to use the presently claimed methionine compounds for the treatment of ototoxicity.

Furthermore, Applicant is silent as to demonstrating any evidence, discussion or results in support of their claim to treat neurotoxicity and reduced survival using any member of the genus of compounds defined in present claim 1. In the absence of any such evidence or discussion either in the present disclosure or in the presently submitted 1.132 Declarations of K. Campbell and P. Sunkara, it is noted that Applicant has failed to provide sufficient direction as to how to use the presently claimed methionine compounds for the treatment of such disorders and the specification, therefore, is properly found to lack adequate enablement for these aspects of the

invention.

Applicant, however, has shown evidence in the Declaration of P. Sunkara that the presently claimed methionine compounds have efficacy in increasing the survival of jejunal crypt cells, which, in turn, have an effect on treating oral mucositis resulting from radiation exposure. However, the mere demonstration that the presently claimed methionine compounds have efficacy in the treatment of oral mucositis is not sufficient to claim the entire genus of gastrointestinal disorders, considering the breadth and disparity of conditions that fall under such a category, particularly in the absence of any reasonable or soundly scientific reasoning as to why the increased survival in mice jejunal crypt cells would be representative of the same or substantially similar efficacy in treating any gastrointestinal disorder known in the art. For example, the efficacy of a particular compound in the treatment of nausea would not necessarily have the same efficacy in treating intestinal bleeding resulting from ulcerative colitis.

In essence, the issue at hand is whether Applicant has sufficiently enabled the use of the presently claimed methionine compounds for the treatment of any known gastrointestinal disorder. It is unlikely that the mere demonstration of efficacy in mucositis would have been representative of the same or substantially similar efficacy in the treatment of any one of the entire breadth of diseases that could possibly be characterized as disorders of the gastrointestinal system, considering the complexity of many gastrointestinal disorders and the vast differences in etiology and pathophysiological manifestation(s). Clearly, the enablement of one disorder is most certainly not a representative number of species belonging to the genus of "gastrointestinal disorders", in general, and, therefore, is not found to be a showing commensurate in scope with what is presently claimed.

In further response thereto, it is noted that the present disclosure, even when taken in combination with the evidence provided in the Declarations of Kathleen Campbell and Prasad Sunkara, also fails to provide sufficient enablement as to how any one member of the genus of compounds defined in present claim 1, other than D-methionine, could be used to treat ototoxicity, neurotoxicity, alopecia, gastrointestinal disorders or reduced survival.

It is noted that Applicant has demonstrated the use of only one of the genus of methionine or methionine-like compounds defined by present claim 1. In each representative example provided in the Declarations of K. Campbell and P. Sunkara, the compound D-methionine was employed. However, neither the specification nor the Declarations provide any reasonable or sound scientific reasoning as to why the activity observed with D-methionine would also have been representative of each member of the genus of compounds encompassed by the formula defined in present claim 1. Again, considering the breadth of the genus of compounds presently claimed, the mere demonstration of efficacy of one compound (i.e., D-methionine) is certainly not considered to be a representative number of species of the presently claimed genus to entitle Applicant to claim the entire genus of compounds in the absence of any soundly scientific reasoning as to how the efficacy of one such agent would have been reasonably suggestive of the same, or substantially similar, activity of each of the compounds that fall within such a genus.

Given the breadth of what is presently claimed, what is presently disclosed and what is supported by adequate description in the present specification and further described in the submitted Declarations under 37 C.F.R. 1.132 of K. Campbell and P. Sunkara, the skilled artisan would have no alternative recourse but undue experimentation in order to determine how the present invention could be used to treatment the entire breadth of diseases and disorders

presently claimed using any one compound from the genus of compounds presently claimed or even if all or most of the presently claimed compounds would even have efficacy in treating all or most of the presently claimed disorders.

It is reiterated that Applicant has provided sufficient enablement for the use of D-methionine for the treatment of alopecia and mucositis, as evidenced by the Declaration of P. Sunkara.

For these reasons and those already made of record in the previous Office Action dated May 17, 2005 at page 2, rejection of claims 1-9 and 11-29 under 35 U.S.C. 112, first paragraph, remains proper and is **maintained**.

Claim Rejection - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 5-9, 15-17, 20-22 and 29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

The MPEP sets forth the following at §2173:

> "The primary purpose of this requirement of definiteness of claim language is to ensure that the scope of the claims is clear so the public is informed of the boundaries of what constitutes infringement of the patent. A secondary purpose is to provide a clear measure of what applicants regard as the invention so that it can be determined whether the claimed invention meets all the criteria for patentability and whether the specification meets the criteria of 35 U.S.C. 112, first paragraph with respect to the claimed invention." (See MPEP §2173).

The term "about" in the expression "from about 36 hours before said radiation exposure

to about 36 hours after said radiation exposure" as recited in present claim 5, for example (see similar claim limitations in present claims 6-9 and 20), or in the expression "from about 1.0 mg/kg body weight to about 600 mg/kg body weight" as recited in present claim 15, for example (see similar claim limitations in present claims 15-17 and 22), or "at least about 10%" as recited in present claim 21, for example (see also present claim 29), is a relative term that renders the claim indefinite. The expression "about" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and thus one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The use of such a term would invite subjective interpretations of whether or not a particular number, amount or percentage is included in or excluded from the present claims and what degree of variability outside the recited ranges is within the scope of the claims.

Furthermore, the Examiner also has noted the word "from" in present claims 5-9, 15-17, 20 and 22 and the phrase "at least" in present claims 21 and 29. For example, the word "from" in the phrase "from about 36 hours before said radiation exposure to about 36 hours after said radiation exposure" as recited in present claim 5, or "at least about 10%" as recited in present claim 21 indicates that the number of hours is between 36 hours before to 36 hours after or that the supplemental amount administered achieves a blood serum level of greater than 10% of the effective amount. However, the use of the word "about" denotes that the number of hours may be slightly greater or slightly less than 36 before or after said radiation exposure, for example, or slightly greater or slightly less than 10% of the effective amount, for example. Thus, it is not clear which is meant to be the limiting term. It is the Examiner's position that the public would not be informed of the boundaries of what constitutes infringement of the present claims.

For these reasons, the claims fail to meet the tenor and express requirements of 35 U.S.C. §112, second paragraph and are, thus, properly rejected.

Double Patenting

Obviousness-Type Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-9 and 11-29 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting over the method claims of U.S. Patent Application Nos. 10/694,436; 10/694,448; and 11/324,744; and are rejected under the judicially created doctrine of obviousness-type double patenting over the method claims of U.S. Patent Application No. 09/911,195 and U.S. Patent Nos. 6,187,817 and 6,265,386.

This is a provisional double patenting rejection over U.S. Patent Application Nos. 10/694,436; 10/694,448; and 11/324,744; since the conflicting claims of such applications have

not yet been patented.

This is a non-provisional double patenting rejection over U.S. Patent Application No. 09/911,195, since the conflicting claims are in the process of issuing as a United States Patent.

This rejection is directed solely to the claims of the above-cited patent applications that define methods, i.e., the same statutory category of invention.

Due to the number of applicable different patents and patent applications, a detailed analysis of why the presently claimed subject matter would have been an obvious variation over each one of the applicable claims in the various patent applications is not presented, but the rejection set forth below is representative of and applicable to all of the above-cited patent applications, but for the differences in claim numbering.

Claims 1-9 and 11-29 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-41 of U.S. Patent Application No. 11/324,744.

For the following reasons, the presently claimed subject matter would have been obvious not only over such claims, but over each of the applicable claims of the remaining U.S. Patent Applications and U.S. Patents cited above.

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claims because the examined claims is either anticipated by, or would have been obvious over, the reference claims.

Although the conflicting claims are not identical, the claims of the instant patent application and those of the copending patent application are not considered patentably distinct from each other because the present claims render the copending claims obvious.

In particular, it is noted that the present claims clearly provide for the use of a methionine or methionine like compound as defined in present claim 1 for treating ototoxicity. The major difference between the present set of claims and the copending set of claims lies in the fact that the present claims are drawn to the treatment of ototoxicity as it results from exposure to radiation for a time and at an intensity sufficient to result in such a condition, where the copending claims are drawn to the treatment of ototoxicity as it results from exposure to noise for a time and at an intensity sufficient to result in such a condition. While such a difference has been carefully considered, it fails to impart patentable distinction to the copending claims over the present claims because both the present claims and the copending claims are primarily directed to the treatment of ototoxicity. Regardless of how such a condition developed, both the present set of claims and the copending set of claims expressly teaches the same methionine or methionine like compounds for the treatment of the same condition (i.e., ototoxicity).

Furthermore, it is noted that such limitations do not directly impact the host at the time the compounds would have been administered to such a host. In other words, the host required for both the present claims and the copending claims amounts to no more than a patient that has ototoxicity. Whatever other circumstances that such a patient may have been exposed to prior to the treatment to induce such a condition does not impact the execution of the method as presently claimed because such circumstances occurred prior to the execution of the method and, therefore, do not limit the host. Thus, while the present claims and the copending claims may be different in this respect, such a difference does not patentably distinguish the copending claims from the present claims.

Moreover, the determination of the optimum dosage amounts or regimen or route of administration would have been a matter well within the purview of the skilled artisan. Such a determination would have been made in accordance with a variety of factors, such as the age, weight, sex and medical condition of the patient, severity of the condition, pharmacokinetic and pharmacological considerations, such as the activity or efficacy of the compound, toxicological considerations, desired duration of effect, frequency of administration and patient compliance with the regimen. Thus, the discovery of the optimum or workable ranges by route experimentation does not amount to a patentable distinction between the present claims and the copending claims.

Accordingly, rejection of claims 1-9 and 11-29 of the present application is deemed proper over claims 1-41 of U.S. Patent Application No. 11/324,744 and over the method claims of each of the other cited U.S. Patent Applications and U.S. Patents as claiming obvious and unpatentable variants thereof.

Citation of Pertinent Prior Art

It is noted that the prior art made of record in the Information Disclosure Statements submitted by Applicant discloses radioprotective effects of sulfur-containing compounds on cells, the cited references are directed to compounds that fall outside of the scope of the recited compounds or do not anticipate or render obvious the presently claimed method. Furthermore, relevant references that have been located in the prior art do not expressly teach or anticipate the instantly claimed method of treatment, nor do such references provide sufficient motivation to

combine such references to make the instantly claimed method *prima facie* obvious to one of ordinary skill in the art.

The prior art made of record and not relied upon is considered pertinent to Applicant's disclosure. Please reference the following:

(1) U.S. Patent No. 5,122,369 to Dye ("Nutrient Composition for Preventing Hair Loss");

(2) E.P. No. EP 0008171 to Mathur et al. ("Hair Treatment Composition and Method");

(3) U.S. Patent No. 5,137,712 to Kask et al. ("Use of S-Adenosyl-L-Methionine (SAME) to Reverse And/Or Prevent Supersensitivity, Tolerance and Extrapyramidal Side Effects Induced by Neuroleptic Treatment");

(4) E.P. No. EP 0482493 to Le Greca ("Pharmaceutical Compositions Active in the Therapy of Neurological Affections in AIDS Patients, Containing as an Active Principle at Least One Compound Selected from the Group Consisting of S-adenosyl-L-methionine Salt, 5-methyl-tetrahydrofolic Acid, 5-formyltetrahydrofolic Acid");

(5) U.S. Patent No. 5,952,367 to Pak ("Method of Treating Pain Caused by Bursitis, Tendinitis or Arthritis");

(6) U.S. Patent No. 3,941,818 to Abdel-Monem ("1:1 Zinc Methionine Complexes");

(7) U.S. Patent No. 5,053,429 to Hirsch et al. ("Treating Inflammatory pain with Methionine");

(8) E.P. No. EP 0387757 to Maggioni Moratti ("Use of 5'-deoxy-5'methylthioadenosine, S-adenosylmethionine and Their Salts in the Preparation of Pharmaceutical Compositions Favouring Hair Growth in Subjects Suffering from Baldness and Relative Pharmaceutical Compositions"); and

(9) Review Article to Jereczek-Fossa et al. ("Radiotherapy-Induced Ear Toxicity"; *Cancer Treatment Reviews*).

Conclusion

Rejection of claims 1-9 and 11-29 is deemed proper and is **maintained**.

No claims of the present application are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leslie A. Royds whose telephone number is (571)-272-6096. The examiner can normally be reached on Monday-Friday (8:30 AM-5:00 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (571)-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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